Obesity and Diabetes

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This report focuses on a series of lectures that were presented in New York over the past year. Many of the lectures describe aspects of the relationship between both fat and adipocytes and diabetes and were presented at the Mount Sinai Institute. Presenters mentioned here include, among others, Angeliki Georgopoulos, Willa Hsueh, Harold Lebovitz, J. Dennis McGarrry, Gerald Shulman, Michael Schwartz, Joshua Tannenbaum, and Helen Vlassara.

At the Gerald J. Friedman Symposium, New York, NY, on 7 November 1999, J. Dennis McGarry, Dallas, TX, discussed the role of fatty acids (FAs) in glucose homeostasis. He reflected on the difficulty in understanding the interaction among basal hyperinsulinemia, the early increase in insulin response to glucose, the increase in hepatic glucose production, and insulin resistance. A speculation is that the lipid abnormality of high triglyceride and FA levels may underlie the glycemic abnormality (with, perhaps, defects in leptin signaling) in the capacity of muscle to oxidize FAs or in hepatic, β-cell, and adipocyte fat metabolism, which leads to the accumulation of fat in these tissues. There is evidence that muscle fat accumulation is related to insulin resistance (1). By using nuclear magnetic resonance (NMR) proton spectroscopy to measure muscle fat, McGarry observed that there are two types of muscle fat: that which is found within myocytes and that which is found in the surrounding adipose tissue; the former is "massively increased" in type 2 diabetes. McGarry speculated that similar fat accumulations in liver and β-cells contribute to hepatic and islet dysfunction. Muscle fat accumulation may involve abnormal regulation of mitochondrial carnitine palmitate transferase (CPT)-1, which is inhibited by malonyl CoA. The increase in muscle malonyl CoA in diabetes may decrease β-oxidation of fats, with an attendant increase in triglyceride synthesis. This can be replicated with administration of etomoxir, which leads to etomoxir CoA synthesis, thereby decreasing CPT-1 activity and causing insulin resistance that is then exacerbated by triglyceride loading. McGarry pointed out that, under some circumstances, fats lower glucose levels. The increase in circulating free fatty acid (FFA) levels with heparin plus triglyceride emulsion infusion acutely increases insulin responses, whereas nicotinic acid, which decreases FFA levels, is associated with decreased insulin secretion. In the transition from the fed to fasted states, the β-cell becomes dependent on FFAs to respond to a glucose load. Saturated fats have the greatest effect in potentiating the insulin response. Chronically, however, increases in islet fat cause β-cell dysfunction. Thus, lipotoxicity contributes to the insulin deficiency of type 2 diabetes. A potential mechanism of action of thiazolidinediones occurs by decreasing muscle fat accumulation and improving insulin sensitivity, which possibly has an additional effect on β-cell fat to improve insulin secretion. Leptin may affect sympathetic outflow and lead to dispersion of fat from muscle, liver, and pancreas to similarly improve glycemia, whereas leptin deficiency may contribute to insulin resistance. McGarry speculated that approaches of this sort may "prevent the transition from IGT [impaired glucose tolerance] to type 2 diabetes, an exciting challenge."

Rudolph Leibel, New York, NY, discussed the regulation of energy homeostasis at the symposium. Caloric stores are related to a variety of factors, including food intake, energy expenditure, growth, puberty, fertility, and insulin sensitivity and secretion, and "the discovery of leptin [represents] an outgrowth of the efforts to find one of the signals." In all of the mammals studied, the energy required to maintain body weight is ~70 kcal/[body wt]$^{0.75}$; individuals of all species show compensatory increases or decreases in energy expenditure with corresponding changes in caloric intake. The total energy expenditure in humans is 36.4 × fat free mass plus 9.4 × fat mass. Subsequently, as fat mass increases for a given body mass, caloric requirements decrease. When weight is maintained at 10% below basal, the resting energy expenditure decreases 8%, but nonresting energy expenditure decreases 36% with an overall 15% fall in energy expenditure. The fall in nonresting energy expenditure has been directly demonstrated with NMR studies of exercising skeletal muscle, showing a decline in high-energy phosphate consumption after weight reduction. Potential causes include decreased leptin levels and decreased sympathetic tone. Other factors include the thermic effect of feeding and the effect of uncoupling proteins (UCPs) on adipocyte energy release. Thus, after weight loss, energy expenditure is depressed, and "if you integrate that over 6 months to a year, it dooms most of those [who have lost weight] to re-gain." Taking a long-term perspective, humans ingest ~900,000 kcal yearly; a mere 0.15% excess of calories from age 25–55 years will lead to a 20-lb weight gain.

Hypothalamic efferent signals influence both energy intake and expenditure; fat stores provide the primary signals concerning energy stores to the brain. Animals with mutations in the leptin/leptin receptor axis eat more, expend less energy, and store more calories as fat, suggesting that leptin influences all of these systems. Leptin is produced in adipocytes, is increased by insulin and glucocorticoids, and is

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Abbreviations: AGE, advanced glycation end product; AgRP, Agouti-related protein; apo, apolipoprotein; BAT, brown adipose tissue; CHD, coronary heart disease; CNS, central nervous system; CPT, carnitine palmitate transferase; CT, computed tomography; CVD, cardiovascular disease; FA, fatty acid; FFA, free FA; G6P, glucose-6-phosphate; IRS, insulin receptor substrate; MAPK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; MS, metabolic syndrome; NMR, nuclear magnetic resonance; NOS, nitric oxide synthetase; NPY, neuropeptide Y; PAI-1, plasminogen activator inhibitor 1; PI3-K, phosphatidylinositol 3-kinase; POMC, proopiomelanocortin; PPAR, peroxisome proliferator–activated receptor; PVN, paraventricular nucleus; RXR, retinoid X receptor; TZD, thiazolidinedione; UCP, uncoupling protein; WAT, white adipose tissue; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

decreased by catecholamines. It enters the brain by facilitated transport and stimulates hypothalamic signals to suppress food intake and increase sympathetic nervous system activity. Leibel pointed out that leptin provides "a signal of the sufficiency of energy storage." It is therefore less likely to help the individual avoid excess fat than to prevent deficiency, with low levels of leptin leading to hypometabolism, infertility, hunger, and relative growth hormone deficiency. Such decreases in leptin levels are seen within 24 h of initiation of an extreme hypocaloric diet, but they are also seen in weight-reduced individuals with decreased adipocyte stores. Individuals may differ in their thresholds for changes in leptin secretion because of either genetic or acquired differences in insulin or neuropeptide response. It should be noted that a considerable increase in leptin is required to cause hypophagia and hypermetabolism. Thus, leptin treatment may play a role in maintaining reduced weight rather than producing weight loss, because leptin could "trick the brain into thinking there's more fat."

Michael Schwartz, Seattle, WA, suggested at the Friedman symposium that "obesity and diabetes are diseases of the brain" and claimed that the "virtual explosion of CNS [central nervous system] signaling molecules" leads to completely new potential approaches to treating diabetes. The model is characterized by a negative feedback loop; higher fat stores generate humoral signals that change levels of CNS effectors and thereby cause negative energy balance. In the brain, leptin has two complementary actions: it stimulates weight loss and inhibits weight gain. The melatonins are major mediators of leptin's anorectic effects, which are expressed in the arcuate nucleus of the hypothalamus and project to proopiomelanocortin (POMC) receptors in the lateral hypothalamus. POMC agonists cause anorexia, and POMC antagonists cause hyperphagia; the latter observation suggests that there is tonic basal POMC input. Indeed, animals with leptin or leptin receptor deficiency show a decrease in hypothalamic POMC expression. Furthermore, experimental POMC receptor blockade prevents the anorectic response to leptin. Leptin's second action, that of inhibiting weight gain, appears to occur by decreasing the expression of neuropeptide Y (NPY) and other anabolic signals. Leptin-deficient mice have markedly increased hypothalamic NPY levels. Thus, Schwartz showed reciprocal regulation of NPY and POMC in a variety of experimental states, with fasting, uncontrolled diabetes, and leptin or leptin receptor deficiency increasing hypothalamic NPY and decreasing POMC, whereas leptin administration and overfeeding cause the opposite effects. POMC has an endogenous antagonist, the Agouti-related protein (AgRP), which is expressed in the arcuate nucleus, with experimental overexpression or local administration of AgRP causing hyperphagia and obesity. AgRP is coexpressed in NPY neurons, whereas POMC neurons, which are separate, coexpress cocaine-amphetamine–regulated transcript, the precise role of which is less clear. The current concept is that these arcuate nucleus neuropeptides are the main CNS effectors of signals related to energy balance; other peptides that change with leptin excess and deficiency are secondary signals. Signals in the lateral hypothalamus stimulate and those in the paraventricular nucleus (PVN) inhibit food intake. Schwartz pointed out that insulin "was actually the first proposed signal that provides negative feedback to the brain" by entering the brain via receptor-mediated transport with arcuate nucleus receptors leading to NPY suppression, PVN activation, and weight loss. Potential therapeutic approaches may include leptin itself, POMC agonists, and NPY antagonists.

Luciano Rossetti, New York, NY, discussed the relationship between nutrient sensing and insulin action at the symposium. Insulin resistance in type 2 diabetes is associated with genetic, obesity-related, and environmental factors, and almost every experimental model of leptin resistance or deficiency is associated with insulin resistance or actual diabetes. Leptin levels peak at ~40% over baseline at ~2:00 A.M. and also have meal-related changes, which are potential mechanisms of feedback to insulin target tissues. Thus, nutrients may indirectly regulate gene expression in muscle, fat, and liver via an energy-sensing feedback loop involving the leptin/POMC system. Rossetti proposed that the short-term action of leptin may be as a "nutrient-counterregulatory" hormone. Leptin potentiates insulin action, and leptin resistance, as a result of either a decreased ability of nutrients to stimulate leptin biosynthesis or decreased leptin action, may be an important component of the insulin resistance syndrome. Another question concerns whether insulin resistance involves CNS resistance to leptin action.

During his lecture at the Mount Sinai Diabetes Conference on 18 May 2000, Joshua Tannenbaum discussed UCPs, which appear to play a major role in regulating energy expenditure. The mitochondrial transport superfamily includes anion carriers, such as those for ATP/ADP, magnesium, and dicarboxylic acid; cation carriers, including the transporters for ornithine and carnitine; and the UCPs themselves, which lead to heat generation by uncoupling the re-entry of protons from the new formation of ATP. Up until a few years ago, these proteins were thought to act by promoting FA oxidation. There is a transmembrane electrical charge gradient across the mitochondrion with H^+ at greater levels outside. In effect, the mitochondria act as batteries, and UCPs short-circuit the transmembrane electrical charge gradient. UCPs account for ~20% of energy metabolism. UCP-1 was discovered in brown adipose tissue (BAT), which is present only to a minimal extent beyond the neonatal period in humans. In 1997, UCP-2 was found, showing 50% homology with UCP-1 and coded on a locus linked to obesity and hyperinsulinemia. In rodents, UCP-2 is expressed in BAT, kidney, heart, and white adipose tissue (WAT), and it shows regulation by diet; cold exposure and β_3 agonists do not affect UCP-2 but increase UCP-1. A/J mice, which are resistant to diet-induced obesity and diabetes, have twice the UCP-2 expression with high-fat diet compared with the susceptible white B6 mice, which do not show induction of UCP-2 with overeating. UCP-3 shows 73% homology with UCP-2; both are coded on chromosome 11q13, whereas UCP-1 is coded on chromosome 4q31. UCP-3 is mainly expressed in muscle. Half of the increase in energy expenditure with hyperthyroidism is related to proton leak, with thyroid hormones appearing to regulate UCP-3. β_3 agonists increase UCP-3 in WAT.

Experimental data are inconclusive as to whether decreased UCP activity may contribute to diabetes or obesity. UCP-1, UCP-3, and double UCP-1/UCP-3 knockout mice do not develop obesity, perhaps because of a compensatory increase in the other UCPs, such as those reported with the increased UCP-2 and UCP-3 expression in the UCP-1 knockout mice. In humans, three UCP-3 polymorphisms have been described. G→A in exon 6 is associated with increased obesity prevalence but has only been found in one population. UCP-1 mutations and β_3 adrenergic receptor mutations have also been described and may be associated with lesser

degrees of weight loss on a calorie-restricted diet and a greater weight gain on weight-maintaining diet. When obese patients are maintained at 20% weight loss, UCP-2 levels increase whereas UCP-3 levels decrease in muscle and WAT. It is worth noting that the UCP-3 promoter has a peroxisome proliferator–activated receptor (PPAR)-γ/retinoid X receptor (RXR) response element as well as a thyroid hormone response element. Retinoic acid increases UCP-1 and decreases UCP-2 and -3. Glucocorticoids reduce all UCP mRNA levels. UCP-2 mRNA increases with increased leptin, though to a varying extent, whereas food-restricted diets do not affect UCP-2 but decrease UCP-1 and -3 levels. Effects of PPAR agonists are of interest. Administration of bezafibrate, like fat feeding, increases UCP-3 levels, whereas administration of rosiglitazone increases UCP-1, an effect that may be blocked by bezafibrate.

Gerald Shulman, New Haven, CT, spoke at the Mount Sinai Institute on 13 April 2000. By using NMR spectroscopy with ^{31}P to measure ATP and glycolytic intermediates and ^{13}C to allow assessment of glycogen and lipids, the incremental change in muscle glycogen during labeled glucose infusion with a hyperglycemic-hyperinsulinemic clamp decreases by 50% in patients with type 2 diabetes. Most nonoxidative glucose metabolism occurs during muscle glycogen synthesis. Because oxidative glucose uptake is similar in individuals with and without diabetes, "the big defect is getting glucose into muscle glycogen." Muscle glucose-6-phosphate (G6P) levels increase from 0.1 to 0.2 mmol/l in nondiabetic individuals during clamp studies but show little change in patients with type 2 diabetes. In insulin-resistant offspring of two parents with type 2 diabetes, G6P levels similarly do not increase. The essential defect is in the GLUT4 glucose transporter. In liver, direct NMR measurement of changes in hepatic glycogen shows that approximately half of basal glucose production derives from gluconeogenesis. After a 24-h fast, basal glucose production increases to 80%, and, after 48 h of fasting, it increases to >95% while glycogenolysis decreases and the gluconeogenic rate is relatively constant. The hepatic glucose production rate has a strong correlation with the fasting blood glucose level. To assess the driving force for hepatic glucose production in glycogenolysis versus gluconeogenesis, Shulman pointed out that patients with type 2 diabetes have approximately half as much liver glycogen as control subjects with half as much glycogenolysis, whereas gluconeogenesis is ~60% greater than that in nondiabetic individuals.

Shulman assessed the effect of exercise. By examining young healthy insulin-resistant offspring to assess whether exercise reversed the defect in glucose transport and phosphorylation, he showed that, after 6 weeks of training, there was an ~60% increase in insulin-stimulated glucose metabolism in these offspring. In control subjects, he noted that a similar increase was seen and, thus, the relative difference remained. To a large degree, nevertheless, the increased response to insulin corrected the abnormalities of the insulin-resistant state. AMP kinase acts as a sensor of muscle energy stores, and an increase in AMP potentially explains the effect of exercise training on the increase in muscle energy stores. Other factors include mitochondrial metabolism. In studies on the mechanism of action of troglitazone, Shulman noted that there was a dose-related increase—though not to normal levels—in glucose uptake in type 2 diabetic patients who were treated with troglitazone. Interestingly, in nondiabetic animal models, there is similarly no increase in insulin action above normal levels. Troglitazone increases glucose oxidation and glycogen synthesis in association with increases in G6P levels during clamp procedures. An important question concerns whether this increase in glucose transport and the other effects of troglitazone are direct or indirect (due to effects on fat cells). Shulman noted that metformin acts principally on hepatic glucose production, whereas troglitazone acts on increasing peripheral glucose uptake. The effect of metformin on the periphery may be due to a decrease in glucose toxicity.

Assessing the mechanisms of insulin resistance in muscle and liver, Shulman noted the inverse relationship between plasma FFA levels and insulin sensitivity. Proton NMR allows measurement of intramyocellular triglyceride levels, which show an even stronger inverse relationship with insulin sensitivity. It is worth noting that the Randle hypothesis suggests that with increasing FFA levels, there will be increased mitochondrial acetyl CoA levels via pyruvate dehydrogenase inhibition, which would inhibit hexokinase via G6P accumulation. Contrary to expectations, during heparin/lipid emulsion infusion to increase FFA levels and during a hyperinsulinemic-hyperglycemic clamp, decreased insulin sensitivity, decreased muscle glycogen, and decreased G6P levels are observed. These findings suggest that FFAs actually act by interfering with glucose transport and, subsequently, by decreasing intracellular glucose levels. Thus, the defect is indeed due to decreased transport. Potential sites of action include FFA interference with GLUT4 translocation or activity or with the insulin-signaling cascade at the insulin receptor, at insulin receptor substrate (IRS)-1 or -2, or at phosphatidylinositol 3-kinase (PI3-K), which increases during the hyperinsulinemic clamp. This increase is abolished by FFAs as a decrease in IRS-1 tyrosine phosphorylation and an increase in IRS-1 serine phosphorylation also occurs. Protein kinase C-τ, a known serine kinase, is activated. Shulman noted that c-Jun kinase also activates serine phosphorylation of IRS-1, suggesting that the mitogenic insulin pathway decreases activity of the metabolic pathway. In mice that do not express adipose tissue, there is insulin resistance in muscle and liver with decreased PI3K signaling but with markedly increased muscle and liver triglyceride levels. When fat is transplanted, the glucose metabolism defect is normalized, and tissue triglycerides are reduced to normal levels. Shulman suggested that the thiazolidinediones (TZDs) may act by decreasing muscle and liver triglyceride levels. In mice with increased levels of lipoprotein lipase specifically expressed in liver or muscle, the respective triglyceride levels are increased with insulin resistance, further suggesting increased intracellular triglyceride to contribute to the abnormal glucose homeostasis of type 2 diabetes.

Harold Lebovitz, New York, NY, discussed the interactions between abdominal obesity and β-cell defects in a lecture at the Mount Sinai Medical Center on 9 March 2000. Insulin resistance is seen in 50–90% of type 2 diabetic patients. Lebovitz suggested that the variation reflects different degrees of visceral obesity, which leads to an increased risk of cardiovascular disease (CVD), whereas hyperglycemia is related to the β-cell defect. In thin (BMI <24 kg/m^2) patients with type 2 diabetes, insulin resistance is infrequent; those patients with a BMI >28 kg/m^2 typically have insulin resistance. Ohlson et al. (2) matched insulin-resistant and insulin-sensitive patients with the same degree of obesity, and found that fasting insulin levels were almost twice as high in the former group, who also had low HDL cholesterol and high triglyceride levels (2). Patients with a low waist-to-hip ratio

(WHR) infrequently have diabetes, regardless of BMI, whereas both the BMI and WHR show association with CVD outcome (3). Patients matched for total body fat levels show increasing insulin and triglyceride levels and decreasing HDL cholesterol levels with higher proportion of visceral fat (4). A number of measures of regional fat have been proposed, including skinfold measurement, waist circumference, WHR, and computed tomography (CT) and magnetic resonance imaging (MRI) scanning. MRI measures of intramuscular and intrahepatic fat have the potential to be extremely useful, and measuring waist circumference appears to be more useful than measuring WHR (5,6). Lebovitz showed CT fat measurement studies in which intra-abdominal fat strongly correlated with insulin resistance and triglyceride levels in a curvilinear relationship in which the degree of insulin resistance plateaued above a certain level. Interestingly, leptin correlates more closely with subcutaneous fat than with visceral fat. Waist circumferences <94 cm (38 inches) and 80 cm (34 inches) in men and women, respectively, appear to convey the lowest degree of risk (7). Visceral fat constitutes ~2.5% of body weight in insulin-sensitive individuals and 4.5% of body fat in insulin-resistant individuals (8,9). In women, total body fat is ~80% greater than that in men, but visceral fat mass is similar. Southeast Asian populations show relatively low BMI but increased visceral fat, which explains their increased risk of diabetes and CVD. Thus, at a BMI of 24 kg/m^2, 75% of individuals from such ethnic groups display insulin resistance. TZDs, however, appear to decrease abdominal fat by ~20%, even though they increase total body fat by ~4.5% (10). Subsequently, some of the benefits of TZD administration may be similar to those of metformin, which decreases total body and visceral fat. Lebovitz speculated that visceral fat has particular adverse effects because of an increased release of FFAs, which may interfere with insulin action in both muscle and liver.

Jack Gerich, Rochester, NY, and Henry Ginsberg, New York, NY, debated at the Metropolitan Diabetes Society on 29 February 2000. Their debate focused on whether insulin deficiency or insulin resistance is of primary importance in the development of type 2 diabetes (Gerich expressed similar ideas to those suggested by Lebovitz). Ginsberg, who argued for a primary role of insulin resistance, stressed the difficulty in determining whether insulin sensitivity or resistance is primary, particularly because existing treatments are incomplete. More important, he stated, one should ask whether both are needed for type 2 diabetes. Certainly, insulin deficiency causes diabetes, and one could always argue that if β-cells could respond to any present degree of insulin resistance, then diabetes would not exist. Extensive literature shows that insulin resistance is present in type 2 diabetes and is only partially responsive to glucose-lowering treatment. Both relatives of patients with type 2 diabetes and individuals with impaired glucose tolerance have evidence of insulin resistance. Those studies following offspring of two parents with diabetes are among the most important studies presently being conducted. In one such study, Warram et al. (11) showed that 25 of 155 such individuals developed diabetes over a 13-year follow-up period. The baseline fasting insulin was two times higher among those who did versus those who did not develop diabetes. Levels of first-phase insulin release were similar in the two groups, which suggests insulin resistance rather than deficiency to be the earliest abnormality. Neither fasting glucose nor weight contributed significantly to the development of diabetes in multivariate analyses, suggesting that insulin deficiency may be the result of the underlying insulin-resistant state. Other studies have shown great heterogeneity between populations. Offspring of diabetic patients with high and low fasting insulin have higher and lower insulin levels, suggesting the heritability of insulin resistance. Gerich, however, argued that much of the insulin resistance in the population is due to obesity—the genetic predisposition to insulin resistance actually represents the genetic predisposition to obesity. He pointed out that β-cell dysfunction is always required for the development of diabetes; insulin resistance is not. Patients with type 2 diabetes have a marked decrease in insulin response. Gerich suggested that those individuals without obesity, particularly without an excess of abdominal fat, have insulin sensitivity similar to that seen in control subjects, particularly when controlling for insulin levels during "clamp" studies. He argued against the view that insulin resistance is the major genetic factor in subjects with subsequent β-cell exhaustion. Gerich's studies have shown a strong negative correlation between the initial insulin response to glucose and the degree of increase in glucose 2 h after an oral load. Thus, administration of somatostatin to normal subjects for the first 30 min of a glucose tolerance test simulates both the initial and the subsequent pattern seen in individuals with impaired glucose tolerance. Furthermore, studies of first-degree relatives more often show insulin deficiency than insulin resistance. Evaluation of monozygotic twins given a lifetime 80% diabetes concordance shows that when only one of the twins has diabetes, the difference lies not in insulin sensitivity but in the diabetic twin having a decrease in first-phase insulin release. To address the questions of reversibility and determination of therapeutic response, Gerich suggested that, with diet and weight loss, insulin sensitivity can be improved, but that insulin response shows little change.

Scott Grundy, Dallas, TX, discussed the insulin resistance syndrome on 1 June 2000 at the Mount Sinai Diabetes Conference. He suggested that high FFA levels may cause the syndrome; secondary increases in tissue triglyceride then affect hepatic and muscle insulin sensitivity and β-cell insulin production. Grundy deemed this condition the "metabolic syndrome" (MS). He pointed out that, "when it comes down to managing patients, [...] there is less consensus" concerning the components and the pathogenesis of the syndrome, which consists of atherogenic dyslipidemia with high triglyceride, low HDL cholesterol, and small LDL particles; hypertension and insulin resistance with or without glucose intolerance; and prothrombotic and proinflammatory states. Grundy deemed LDL cholesterol "the primary driving force" for atherosclerosis, but acknowledged that "once a population has a certain level of LDL, other factors come into prominence." In particular, an important cause of artherosclerosis is abdominal obesity, which leads to high plasma FFA levels (12). The reproduction of the MS by lipodystrophy further suggests abnormalities of tissue triglyceride stores to underlie these insulin-resistant states. Grundy pointed out that clinical manifestations of the MS vary in different populations. Caucasians mainly show dyslipidemia, African populations show hypertension, Native Americans show hyperglycemia, and South Asians show both hyperglycemia and accelerated coronary heart disease (CHD), whereas East Asian populations appear partially protected. With decreased physical activity resulting in increased prevalence of the syndrome, the MS is "increasingly a precursor of CHD and stroke." Weight reduction and physical activity are primary com-

ponents of treatment, with the former resulting in increased insulin sensitivity (13). Moreover, surgical treatment of extreme obesity is associated with falls in blood pressure of ~10 mmHg and increases in HDL cholesterol of ~33% (14). Grundy showed data that LDL cholesterol is lowered similarly with low-fat and high–monounsaturated fat diets, but that HDL cholesterol decreases and triglycerides increase with the low-fat but not with the high–monounsaturated fat diets when both are kept at weight-maintaining levels. Of course, the benefits of a high–monosaturated fat diet must be balanced with the need for weight reduction, which is more readily achieved with hypocaloric diets not containing monounsaturated fats. While discussing proinflammatory factors, which Grundy considered to be "intriguing and not fully understood," he mentioned that obesity itself may be proinflammatory and that markers of inflammation are associated with CHD (15). C-reactive protein levels have an additive risk to that of increasing the cholesterol-to-HDL ratio (16). Grundy suggested that vitamin E may be useful for treatment of both the prothrombotic and the proinflammatory state. There may be a role of antibiotic treatment for the latter, based on the concept of infection in the arterial wall. Statins are important in patients with the MS and high LDL levels, and recent studies suggest that pravastatin lowers C-reactive protein levels as well. Fibrates act on PPAR-α, regulate hepatic nuclear factor-4, and decrease apolipoprotein (apo) C3 synthesis, which leads to increased VLDL catabolism. The Helsinki Heart Study showed that gemfibrozil reduced CHD end points in patients with hypertriglyceridemia. Furthermore, the VA-HIT (Veterans Affairs Cooperative Studies Program–High-Density Lipoprotein Cholesterol Intervention Trial) studied "perfect examples of the MS" and was able to increase HDL cholesterol levels by 7.5% and lower triglyceride levels by 24.5% with a 21–27% decrease in CHD and stroke over the 7-year study period. Grundy suggested that in patients with type IIb dyslipidemia, administration of fenofibrates may be more effective than statins and that statin-gemfibrozil combination treatment "could prove [to be] a rational approach." Given the 1% risk of myositis, however, caution is needed. He also stated that "the results look very good" for low-dose niacin in combination with statins, although there is potential for hyperglycemia in diabetic patients. Finally, treatment of insulin resistance with PPAR-γ agonists and metformin "must be one of the most promising" approaches, with the former agents in particular appearing to act by lowering FFA levels and having triglyceride and HDL effects similar to those of fibrates.

On 20 April 2000, Angeliki Georgopoulos, Minneapolis, MN, spoke at the Mount Sinai Diabetes Conference on postprandial lipidemia in diabetes. Atherosclerosis accounts for 60–75% of mortality in patients with type 1 diabetes aged >20 years, with mortality rates 2–4 times those of nondiabetic individuals, even when excluding patients with nephropathy. Despite their normal fasting lipid values, they exhibit an atherogenic state. "Maybe," she suggested, "there are hidden factors," recalling the suggestion of Zilversmit in the 1970s that atherogenesis is a postprandial phenomenon (17), because patients with diabetes spend most of the day in the postprandial state. Epidemiological data support the association with atherosclerosis of triglyceride-rich lipoproteins derived from chylomicrons. Chyomicron remnants produce greater macrophage uptake in the sterol-loaded state via specific receptors, the LDL-related protein receptors, which account for approximately half of chylomicron uptake. Plasmapheresis of patients with type 1 diabetes after fat loading shows that they produce particles with decreased uptake of both chylomicrons and remnants due to decreased tissue uptake rather than decreased lipolysis. The remnant particles have increased cholesterol and decreased phospholipids. Furthermore, incubation of macrophages with the particles isolated from patients with type 1 diabetes shows increased cholesterol ester accumulation; the process of lipid uptake lasts >7 h rather than peaking at 4 h in nondiabetic control subjects. Low-fat diets and statins are helpful in treating type 1 diabetes, although the question of whether postprandial lipids should specifically be measured and treated has not been addressed. In type 2 diabetes, dyslipidemia, obesity, and abnormal postprandial lipids are present with increased VLDL production, perhaps because of increased FFA and glucose levels. Georgopoulos addressed the question of whether there is increased intestinal triglyceride-rich lipid production by studying the common genetic abnormality of fatty acid binding protein 2. This 15-kDa protein binds long-chain fatty acids and is only found in the intestine. The Ala54→Thr mutation is present in one-third of the normal population, having 10% homozygosity. This mutation leads to increased FA uptake by intestinal epithelial cells and a two- to fourfold increase in intestinal triglyceride secretion. Georgopoulos showed data from a study of 287 type 2 diabetic patients, of whom 108 and 31 were heterozygous and homozygous, respectively. Interestingly, the mutation in this group was associated with increased triglyceride and non-HDL cholesterol levels in a dose-related fashion. These patients showed increased postprandial triglyceride as well as increased fasting levels, with the elevation mostly in chylomicron versus VLDL particles. In contrast, in nondiabetic populations and in patients with type 1 diabetes, fasting lipid levels are not increased, although postprandial lipids have not been thoroughly studied.

Mitchell Roslin, New York, NY, discussed surgical treatment of obesity at Mount Sinai on 17 February 2000. Obesity surgery has become a successful approach to treatment, with two approaches having been used. The induction of malabsorption with jejeunoileal bypass was initially recommended, but caused hepatic dysfunction. Currently, obesity is treated with gastric restriction surgery, which Roslin described as "taking a 20-gallon tank and making a 2-gallon tank." Gastric surgery approaches include vertical-banded gastroplasty, which is associated with a 25–30% failure rate and causes fixed obstruction with the potential for esophageal dysmotility syndromes, and gastric bypass, which he recommended as being the best method currently used. Both open and laparoscopic approaches are used, and somewhat higher complication approaches have been described with the latter. Gastric restriction results in a form of "forced behavior modification"—the ingestion of anything more than a small meal causes nausea and vomiting. Maximal weight loss is observed at 6–9 months, with half-maximal weight loss maintained at a 10-year follow-up. Furthermore, comparison of operated versus nonoperated patients indicated marked reduction in mortality and improvement in emotional as well as medical status with treatment. Roslin noted the importance of vagal afferent impulses in satiety, recalling the observation that vagotomy prevents the decrease in food intake caused by cholecystokinin in animal models. Vagal nerve stimulation is currently used clinically for the treatment of seizure disorders. Roslin showed the results of studies of chronic bilateral vagal nerve stimulation in dogs, which showed a decrease in food intake and

thereby suggested a potential use for treating obesity.

Willa Hsueh, Los Angeles, CA, spoke on insulin resistance and vascular disease at Mount Sinai on 27 January 2000. Increased plasminogen activator inhibitor-1 (PAI-1) is seen with increasing degrees of insulin resistance, and both insulin and angiotensin levels are associated with levels of PAI-1, which is produced locally in sites of atherosclerotic vascular disease. Thus, the question concerning the role of hyperinsulinemia in the atherosclerotic process arises. Hsueh recalled the two major cellular pathways of insulin action. The first pathway involves IRS 1–4 and leads to PI3K activation, in turn resulting in glucose metabolism, particularly with increased glucose transport. Endothelial nitric oxide synthetase (NOS) activation also involves this pathway, which is potentially an antiatherosclerotic process. The other pathway leads to activation of mitogen-activated protein kinase (MAPK), which leads to a variety of anabolic effects. These effects include vascular smooth muscle growth and production of PAI-1, the vasoconstrictor endothelin, and a number of chemoattractants that potentially act in a proatherosclerotic fashion. Insulin resistance is defined by the defect in the glucose metabolism arm of the first pathway, but this association does not imply resistance in the proatherosclerotic pathway. Insulin sensitizers, such as the TZDs, turn on glucose metabolism, and a number of studies suggest increased NOS activity with this treatment. Individuals with insulin resistance show a defect in endothelial NOS, which further supports this concept.

Steps involved in macrophage migration into the arterial wall include attachment, which doesn't involve MAPK; locomotion, which involves MAPK phosphorylation of myosin light-chain kinase in the cytosol; and invasion, which appears to be a MAPK-related pathway involving metalloproteinase activation. Antisense nucleotides for several MAPKs inhibit their expression and the migration of vascular smooth muscle cells. Similarly, the agent PD98059 inhibits MAPK pathway activation and vascular cell migration. Hsueh showed that both of these approaches block the growth-promoting action of insulin on the vasculature. The TZDs activate the nuclear PPAR-γ–RXR heterodimer. Both PPAR-γ and RXR-α mRNA are present in macrophages and vascular endothelial and smooth muscle cells. PPAR-γ is also expressed in human coronary lesions in both vascular smooth muscle cells and macrophages and is upregulated in vascular cells of injured tissue. PPAR-γ ligands inhibit platelet-derived growth factor–induced migration in human coronary artery smooth muscle cells and TZD concentrations similar to those achieved by oral treatment. MAPK phosphorylation of transcription factors are inhibited by TZD, leading to decreased growth and migration, whereas TZD does not inhibit MAPK pathway activation per se. Furthermore, TZD does not affect phosphorylation of myosin light chains. Pretreatment of animals with troglitazone 4 days before balloon injury of the aorta results in a decrease in intimal hyperplasia. A study with intravascular ultrasound showed that 14 patients undergoing angioplasty who were treated with troglitazone had 28% intimal hyperplasia at 6 months, whereas 12 patients who were not treated with troglitazone had 49% hyperplasia. Hsueh noted that the initiation of atherosclerosis involves both LDL entry and oxidation and an inflammatory component of monocyte adherence, which leads to uptake into the vessel wall. A study in her laboratory showed that a PPAR-γ ligand inhibited migration of monocytes, another MAPK-modulated process. With high-fat and high-fructose diet models of atherosclerosis, troglitazone attenuated lesion formation and decreased macrocyte infiltration. Troglitazone also inhibited the MAPK-directed process of vascular proliferation under stimulation by vascular endothelial growth factor and is being studied in models of proliferative retinopathy.

Helen Vlassara discussed the development of glycation, an aspect of the biochemistry of glucose toxicity, at Mount Sinai on 14 October 1999 and 16 March 2000, stressing that the Diabetes Control and Complications Trial showed that "glucose itself always plays a major role" in organ damage in diabetes. Though it was not directly related to obesity and adiposity, this line of inquiry has fascinating implications for a new approach to dietary treatment of diabetes. Glycation and glycoxidation are continuous processes based on the reversible binding of glucose to amino groups, thereby leading to the reversible formation of Schiff bases, the more slowly reversible formation of Amadori products, and the irreversible formation of advanced glycation end products (AGEs). AGEs "contain a myriad of chemical structures." These involve amino groups of proteins, as well as phospholipid AGEs, which initiate lipid oxidation and cause release of free radicals. Plasma AGE-apoB correlates with arterial tissue AGE in nondiabetic individuals with atherosclerosis. In diabetic patients, skin biopsy shows increased collagen AGE-links to correlate with retinopathy and nephropathy. Thus, diabetes increases a process already pathogenic in individuals without diabetes. AGEs can cause irreversible cross-linking, oxidative changes, changes in enzyme activities, production of reactive oxygen species, impairment of antioxidant systems, inactivation of nitric oxide, DNA modification, and cellular inflammatory effects by means of cytokine induction. Two metabolic disposal mechanisms are available for AGEs (either cycling to "glycotoxins" or the production of nonreactive AGEs), which are excreted in the kidneys, with renal impairment leading to accumulation of these products and AGE peptides that displayed toxicity to collagen and LDL. AGE administration in animal models has effects similar to cholesterol feeding (increased aortic intimal width and fat content); lipids and AGEs together cause additional effects. Thus, a number of disease states, including diabetes, dyslipidemia, and renal insufficiency, interact with the effects of AGEs. Another important factor is cigarette smoking, which increases serum and tissue AGE levels. Curing of tobacco involves drying under heat in the presence of sugar, which results in a very high AGE content when ingested. AGE-modified LDL levels double with tobacco use. AGE content of food similarly increases with broiling and, to a lesser extent, baking or frying, though not as markedly with boiling or steaming. Cooked meats show the highest AGE content. Approximately 10% of dietary AGEs are absorbed, of which 65% is retained in individuals without diabetes and 97% is retained in individuals with both diabetes and renal insufficiency. Low dietary AGEs prevent the development of renal disease in animal models of diabetes and lower serum AGE levels in humans; they may prove to offer important therapeutic benefits.

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